

REMARKS

In the Office Action, claims 20-23, 42 and 44 were withdrawn from consideration. Claims 1-19, 24-41, 43 and 45-47 were considered and rejected under 35 U.S.C. § 112, first and second paragraphs, 35 U.S.C. § 102, and 35 U.S.C. § 103. The Office Action also raised minor objections to the specification and claims. Applicants have canceled claims 3, 9, 10, 26-28, 30-33, 38-41 and 43 without prejudice to their subsequent reintroduction into this or a subsequently filed continuation application. Claims 1, 2, 4, 12, 18, 24, 25, 29, 34-36, and 45-47 have been amended. Upon entry of this paper, claims 1, 2, 4-8, 11-19, 24, 25, 29, 34-37 and 45-47 will be pending in the application.

Reconsideration and withdrawal of all of the outstanding objections and rejections is respectfully requested in view of the present claim amendments, remarks, and accompanying submissions.

Drawing and Claim Amendments:

Substitute Figure 5

A substitute Figure 5 is submitted herewith. A marked-up copy of Figure 5 is also submitted showing the proposed change in red. The substitute Figure 5 includes a legend that indicates what the different plot characters are. The black diamonds represent results for PBS. The filled circles represent results for KS-IL2. The open circles represent results for KS-(K-A)-IL2.

Applicants submit that basis for this amendment can be found in the specification, *inter alia*, in Example 13 on page 30. Example 13 describes an experiment where mice were treated with PBS, KS-IL2, or KS-IL2 with a Lys to Ala mutation (see, for example, lines 11-18 on page 30). Example 13 states on line 19 of page 30 that “[T]he results of one such experiment are shown in Figure 5.” Example 13 further states on lines 24-27 of page 30 that “black diamonds indicate average tumor volumes in mice that were injected with PBS ...” and “[F]illed circles indicate average tumor volumes in mice treated with 10 micrograms of KS-IL2gamma1.” Applicants therefore submit that one of ordinary skill in the art would understand that the open circles in Figure 5 indicate the average tumor volumes for the remaining experimental condition,

namely treatment with KS-IL2 with a Lys to Ala mutation (indicated as KS-(K-A)-IL2 in the proposed legend for substitute Figure 5, in conformance with the nomenclature of Figure 4). Applicants submit that this amendment is further supported by the description of the results for KS-(K-A)-IL2 in Example 13. See for example lines 22-24 on page 30, where the description of tumor shrinking in response to treatment with KS-(K-A)-IL2 corresponds to the time course shown by the open circles in Figure 5. Therefore, Applicants respectfully submit that the proposed change to Figure 5 is supported by the description of Figure 5 in the specification and introduces no new matter.

Claim Amendments

The claims are amended to further clarify the claimed subject matter. Basis for the claim amendments can be found in the specification, including the claims as originally filed.

Specifically, claim 1 is amended to recite an antibody-based fusion protein comprising an N-terminal immunoglobulin (Ig) chain linked to a C-terminal non-Ig protein, wherein the antibody-based fusion protein comprises at least a) an amino acid alteration within 10 amino acids from the C-terminus of the N-terminal Ig chain, or b) an amino acid alteration within 10 amino acids from the N-terminus of the C-terminal non-Ig protein, and wherein the fusion protein has a longer circulating half-life *in vivo* than a corresponding fusion protein without the amino acid alteration of a) and/or b). Basis for amended claim 1 can be found in the specification, *inter alia*, at page 11, lines 3-24. Applicants submit that this amendment introduces no new matter.

Claim 12 is amended to clarify that the substantially reduced binding affinity of the Ig chain for an Fc receptor is relative to the binding affinity of an unaltered IgG1 for the Fc receptor. Basis for amended claim 12 can be found in the specification, *inter alia*, at page 4, line 19, through page 5, line 4. Applicants submit that this amendment introduces no new matter.

Claims 2, 4, 18, 25, 29, 34-36, and 45-47 are amended to conform with the amendment of claim 1, amend dependencies, and address minor informalities to clarify the claimed subject matter. Applicants submit that these amendment introduce no new matter.

Remarks Regarding Objections and Rejections:

Defective Oath or Declaration

The Office Action stated that the oath or declaration is defective. In response, Applicants submit a substitute Declaration and Power of Attorney in compliance with 37 CFR 1.67(a). This substitute Declaration does not refer to an amendment filed on 2/9/2001. Therefore, Applicants respectfully request that this objection be reconsidered and withdrawn.

Drawings

The Office Action objected to Figure 5 due to the absence of legend indicating what the different plot characters are. Applicants submit a substitute Figure 5 with a proposed change introducing a figure legend. A copy of Figure 5 showing the proposed change in red is also attached. As discussed above, Applicants submit that this change introduces no new matter and is supported by the description of Figure 5 in the specification. Therefore, Applicants respectfully request that this objection be reconsidered and withdrawn.

Claim Objections

The Office Action objected to Claim 25 “under 37 CFR 1.75(c) as an improper multiple dependent claim because it depends from another multiple dependent claim.” In response, Applicants have amended claim 25 to depend from claim 1, 2, 5, 6, or 7. Accordingly, claim 25 no longer depends from another multiple dependent claim. Therefore, Applicants respectfully request that this objection be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. §112, second paragraph

The Office Action rejected claims 1-19, 24-25, 36-37, 39-40, 43, and 45-47 under 35 U.S.C. §112, second paragraph, as being indefinite.

Specifically, claim 1 is allegedly confusing by reciting “a junction point.” Without acquiescing to this rejection, Applicants have amended claim 1 to remove the reference to “a junction point” and to recite an antibody-based fusion protein comprising an N-terminal immunoglobulin (Ig) chain linked to a C-terminal non-Ig protein, wherein the antibody-based fusion protein comprises at least a) an amino acid alteration within 10 amino acids from the C-terminus of the N-terminal Ig chain, or b) an amino acid alteration within 10 amino acids from

the N-terminus of the C-terminal non-Ig protein. As discussed above, this amendment is supported by the application as filed and introduces no new matter. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 9 and 10 were rejected due to the recitation of “various amino acid residues that can be altered in IgG1 or IgG3.” Without acquiescing to the rejection, claims 9 and 10 have been canceled without prejudice. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claim 18 was rejected for lack of antecedent basis for “said colony stimulating factor.” In response, claim 18 has been amended to depend from claim 17 which recites a colony stimulating factor. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claim 12 was rejected due to the recitation of “substantially reduced” without indicating what the reduction is in comparison to. In response, Applicants have amended claim 12 to clarify that the substantially reduced binding affinity of the Ig chain for an Fc receptor is relative to the binding affinity of an unaltered IgG1 for the Fc receptor. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claim 36 was rejected due to the recitation of the phrase a “polypeptide is mutated to be an amino acid.” In response, claim 36 has been amended to clarify that the C-terminal amino acid of the N-terminal Ig chain is altered to be an amino acid with a non-ionizable side chain. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 39 and 40 were rejected due to the recitation of “spacer or linker peptide.” Without acquiescing to this rejection, claims 39 and 40 have been canceled without prejudice. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claim 43 was rejected as depending from non-elected claim 42. Claim 43 has been canceled without prejudice. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 45-47 were rejected due to the recitation of the term “near.” In response, claim 45 has been amended to remove the recitation of the term “near.” In addition, claim 45 has been amended to depend from claim 1, thereby reciting an alteration in either a) and/or b) of claim 1

that introduces a hydrophobic or non-polar amino acid. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

In view of the claim amendments and remarks discussed above, Applicants respectfully submit that claims that depend from the above-referenced claims should no longer be subject to rejection under 35 U.S.C. §112, second paragraph.

Therefore, Applicants respectfully request that all the rejections under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. §112, first paragraph

The Office Action rejected claims 1-19, 24-41, 43 and 45-47 under 35 U.S.C. §112, first paragraph. Specifically, the Office Action alleged that “Applicant has not adequately described the genus of fusion polypeptides that are claimed.”

In response, Applicants respectfully submit that the claims as amended recite antibody-based fusion proteins having the following structural characteristics: an N-terminal Ig chain linked to a C-terminal non-Ig protein wherein the fusion protein comprises at least a) an amino acid alteration within 10 amino acids from the C-terminus of the N-terminal Ig chain, or b) an amino acid alteration within 10 amino acids from the N-terminus of the C-terminal non-Ig protein. Applicants respectfully submit that useful amino acid alterations are disclosed in the specification, *inter alia*, on pages 9-15, and in the Examples. The claims recite that the fusion protein has a longer circulating half-life *in vivo* than a corresponding fusion protein without the amino acid alteration. Applicants’ specification discloses that useful alterations increase the circulating half-life of a fusion protein of the invention. In addition, Applicants’ specification discloses specific examples that illustrate an increased circulating half-life *in vivo* (see Example 9, *inter alia*). Accordingly, Applicants respectfully submit that the amended claims comply with the requirements of 35 U.S.C. §112, first paragraph.

In view of the claim amendments and remarks discussed above, Applicants respectfully submit that claims that depend from the above-referenced claims should no longer be subject to rejection under 35 U.S.C. §112, first paragraph.

Therefore, Applicants respectfully request that all the rejections under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. §102

The Office Action rejected claims 26-27, 30, 34-35 and 38 under 35 U.S.C. §102(a) as anticipated by Gillies et al. (WO 99/43713). Claims 26-27, 30, and 38 have been canceled without prejudice, and claims 34-35 have been amended to depend from claim 1 which was not rejected as anticipated by Gillies et al. (WO 99/43713). Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

The Office Action provisionally rejected claims 26-27, 30, 34-35 and 38 under 35 U.S.C. §102(e) as being anticipated by copending Application No. 09/256,156. As discussed above, claims 26-27, 30, and 38 have been canceled without prejudice, and claims 34-35 have been amended to depend from claim 1 which was not rejected as anticipated by copending Application No. 09/256,156. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Obviousness-Type Double Patenting Rejection: The Office Action provisionally rejected Claims 26-27, 30, 34-35 and 38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/256,156. As discussed above, claims 26-27, 30, and 38 have been canceled without prejudice, and claims 34-35 have been amended to depend from claim 1 which was not rejected over the claims of copending Application No. 09/256,156. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

The Office Action further rejected Claims 26-27, 34-35, 38 and 45-47 under 35 U.S.C. §102(a) as anticipated by Gillies et al. (Cancer Res 59, 2159, 1999). Claims 26-27 and 38 have been canceled without prejudice, and claims 34-35 and 45-47 have been amended to depend from claim 1 which was not rejected as anticipated by Gillies et al. (Cancer Res 59, 2159, 1999). Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

The Office Action also rejected claims 26, 35, and 43 under 35 U.S.C. §102(b) as anticipated by Strom et al. (WO 96/18412) in light of Gillies et al. (WO 99/43713). Claims 26 and 43 have been canceled without prejudice, and claim 35 has been amended to depend from claim 1 which was not rejected as anticipated Strom et al. (WO 96/18412) in light of Gillies et al.

(WO 99/43713). Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

The Office Action also rejected claims 1-2, 5-8, 11-13, 25-26, 35, 43 and 45 under 35 U.S.C. §102(b) as anticipated by Browne et al. (WO 97/00319). As indicated in the Office Action, Browne et al. reports “a fusion protein constituted of a leptin at the N-terminal ... and an Ig Fc at the C-terminal” (see the Office Action at page 10). In contrast, amended claim 1 recites “an antibody-based fusion protein comprising an N-terminal immunoglobulin (Ig) chain linked to a C-terminal non-Ig protein.” Therefore, since claims 26 and 43 have been canceled without prejudice, and claims 35 and 45 have been amended to depend from claim 1, Applicants respectfully submit that the amended claims can no longer be rejected under 35 U.S.C. §102(b) as anticipated by Browne et al. (WO 97/00319). Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

The Office Action also rejected claims 1-2, 5, 7-8, 11-14, 26-33, 35, 39-41, 43 and 45-46 under 35 U.S.C. §102(a) as anticipated by Chang et al. (U.S. Patent No. 5,908,626). As indicated in the Office Action, Chang et al. reports “fusion proteins of IFN beta and Ig Fc at the N- and C-terminals, respectively” (see the Office Action at page 11). In contrast, amended claim 1 recites “an antibody-based fusion protein comprising an N-terminal immunoglobulin (Ig) chain linked to a C-terminal non-Ig protein.” Therefore, since claims 26-28, 30-33, 39-41 and 43 have been canceled without prejudice, and claims 29, 35 and 45-46 have been amended to depend from claim 1, Applicants respectfully submit that the amended claims can no longer be rejected under 35 U.S.C. §102(a) as anticipated by Chang et al. (U.S. Patent No. 5,908,626). Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

The Office Action also rejected claims 1, 5-8, 11-16, 26-33, 35, 39-41, 43 and 45-46 under 35 U.S.C. §102(b) as anticipated by Chang et al. (U.S. Patent No. 5,723,125). As indicated in the Office Action, Chang et al. (U.S. Patent No. 5,723,125) reports “essentially the same invention as that of Chang et al. (U.S. Patent No. 5,908,626), namely “fusion proteins of IFN beta and Ig Fc at the N- and C- terminals, respectively” (see the Office Action at pages 11 and 12). In contrast, amended claim 1 recites “an antibody-based fusion protein comprising an N-terminal immunoglobulin (Ig) chain linked to a C-terminal non-Ig protein.” Therefore, since

claims 26-28, 30-33, 39-41 and 43 have been canceled without prejudice, and claims 29, 35 and 45-46 have been amended to depend from claim 1, Applicants respectfully submit that the amended claims can no longer be rejected under 35 U.S.C. §102(b) as anticipated by Chang et al. (U.S. Patent No. 5,723,125). Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Finally, the Office Action rejected claims 1-2, 5-8, 11-14, 24, 26-33, 35, 39-41, 43 and 45-46 under 35 U.S.C. §102(e) as anticipated by Hermann et al. (U.S. Patent No. 6,100,387). As indicated in the Office Action, Hermann et al. reports “fusion proteins of a chemokine and Fc portion of IgG, which are at the N- and C-terminals respectively” (see the Office Action at page 13). In contrast, amended claim 1 recites “an antibody-based fusion protein comprising an N-terminal immunoglobulin (Ig) chain linked to a C-terminal non-Ig protein.” Therefore, since claims 26-28, 30-33, 39-41 and 43 have been canceled without prejudice, and claims 29, 35 and 45-46 have been amended to depend from claim 1, Applicants respectfully submit that the amended claims can no longer be rejected under 35 U.S.C. §102(e) as anticipated by Hermann et al. (U.S. Patent No. 6,100,387). Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

In view of the foregoing, Applicants respectfully request that all the rejections under 35 U.S.C. §102 be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. §103

The Office Action rejected Claims 1-3, 5-19, 24 and 26 under 35 U.S.C. §103(a) as unpatentable over Gillies et al. (WO 99/43713) in view of Chang et al. (U.S. Patent No. 5,908,626 or 5,723,125). Claims 3 and 26 have been canceled without prejudice.

Applicants submit that the disclosures of Chang et al. (U.S. Patent No. 5,908,626 or 5,723,125) relate to reports of “fusion proteins of IFN beta and Ig Fc at the N- and C- terminals, respectively” as characterized by the Office Action at pages 11 and 12. Therefore, Applicants respectfully submit that the disclosures of Chang et al. do not provide any motivation or suggestion to make alterations in an antibody-based fusion protein comprising an N-terminal immunoglobulin (Ig) chain linked to a C-terminal non-Ig protein, wherein an alteration is within 10 amino acids from the C-terminus of the N-terminal Ig chain and/or within 10 amino acids

from the N-terminus of the C-terminal non-Ig protein, as recited in amended claim 1. Therefore, Applicants respectfully submit that Chang et al. (U.S. Patent No. 5,908,626 or 5,723,125) cannot be combined with Gillies et al. (WO 99/43713) to form the basis for continued rejection of the amended claims under 35 U.S.C. §103(a). Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

In view of the foregoing, Applicants respectfully request that all the rejections under 35 U.S.C. §103(a) be reconsidered and withdrawn.

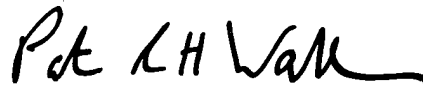
CONCLUSION

Applicant submits that on the basis of the foregoing remarks and claim amendments, claims 1, 2, 4-8, 11-19, 24, 25, 29, 34-37 and 45-47 are in condition for immediate allowance. Accordingly, Applicant respectfully requests entry as such. Should further issues of patentability be determined to exist, the Examiner is respectfully requested to contact the undersigned by telephone to expedite prosecution of this application.

Date: December 30, 2002
Reg. No. 41,418

Tel. No.: (617) 248-7240
Fax No.: (617) 248-7100

Respectfully submitted,



Patrick R.H. Waller, Ph.D.
Attorney for Applicants
Testa, Hurwitz, & Thibeault, LLP
High Street Tower
125 High Street
Boston, Massachusetts 02110

MARKED-UP CLAIMS SHOWING AMENDMENTS FOR U.S.S.N. 09/780,668

1. (Amended) An antibody-based fusion protein comprising an N-terminal immunoglobulin (Ig) chain linked to a C-terminal non-Ig protein [via a junction point], wherein said antibody-based fusion protein comprises at least one of:

a) an amino acid alteration within 10 amino acids from the C-terminus of said N-terminal Ig chain; or, [said junction point, in said Ig chain or said non-Ig protein,]

b) an amino acid alteration within 10 amino acids from the N-terminus of said C-terminal non-Ig protein;

and wherein said antibody-based fusion protein has a longer circulating half-life *in vivo* than a corresponding antibody-based fusion protein without said amino acid alteration.

2. (Amended) The fusion protein of claim 1 wherein said [the] amino acid alteration increases the hydrophobicity of said antibody-based fusion protein.

4. (Amended) The fusion protein of claim 1[, or 2 [or 3] wherein said alteration changes the C-terminal amino acid of the Ig chain.

12. (Amended) The antibody-based fusion protein of claim 7, wherein said Ig chain has substantially reduced binding affinity for a Fc receptor selected from the group consisting of FcγRI, FcγRII and FcγRIII, when compared to the binding affinity of an unaltered IgG1 for said Fc receptor.

18. (Amended) The antibody-based fusion protein of claim 17 [11], wherein said colony stimulating factor is a granulocyte-macrophage colony stimulating factor.

24. (Amended) The fusion protein of claim 1 further comprising a linker between said Ig chain and said non-Ig protein.

25. (Amended) The fusion protein of claim 1, 2, [4,] 5, 6, or 7, wherein said alteration is a substitution of one or more amino acids.

29. (Amended) The fusion protein of claim 1 [26] comprising a first mutation in the C-terminal portion of said first polypeptide and a second mutation in the N-terminal portion of said second polypeptide.
34. (Amended) The fusion protein of claim 1 [26] wherein said Ig chain is IgG1.
35. (Amended) The fusion protein of claim 1 [26] wherein said alteration [mutation] is selected from the group consisting of point mutations, deletions, insertions, and rearrangements.
36. (Amended) The fusion protein of claim 4 [34] wherein the C-terminal amino acid [residue] of said N-terminal Ig chain [first polypeptide] is altered [mutated] to be an amino acid with a non-ionizable side chain.
45. (Amended) The fusion protein of claim 1[, 26, or 36], wherein said alteration introduces [having] a hydrophobic or non-polar amino acid [introduced via addition or substitution at or near said junction].
46. (Amended) The fusion protein of claim 45, wherein said hydrophobic or non-polar amino acid is selected from the group consisting of Leu, [Ala,] Trp, and Gly.
47. (Amended) The fusion protein of claim 46, wherein said hydrophobic or non-polar amino acid is Ala.



attache
Paper #12

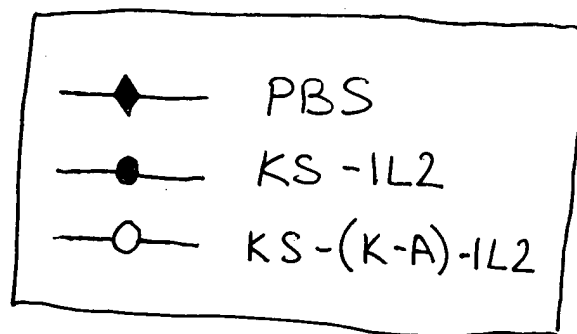
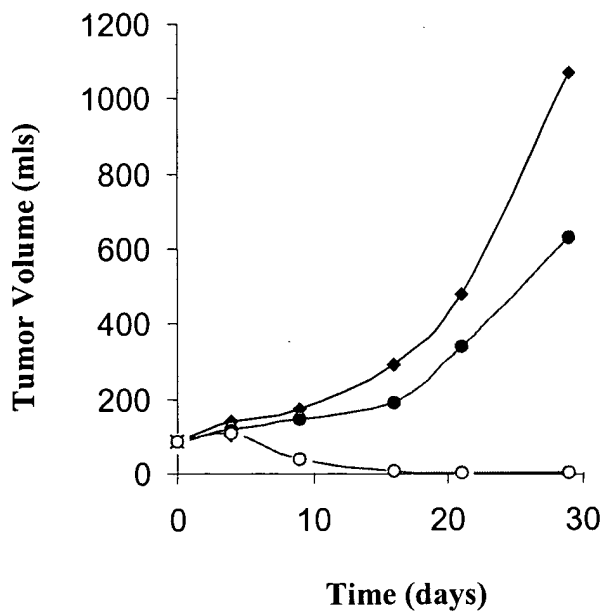


Figure 5